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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GODDARD, LAURA B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,698	HUNG ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *24,27-40 and 43-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-23,25,26,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/15/05 2/15/05*. 1/12/05, 7/16/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed March 3, 2006 in response to the Office Action of February 13, 2006 is acknowledged and has been entered. Applicants elected Group IV (claims 12-26, 41 and 42) drawn to a method comprising administering to a cell a Bik polypeptide having an amino acid substitution. Applicants elected the species of Bik polypeptide comprising an amino acid substitution at both Thr^{33} and Ser^{35}, cancer as the proliferative disorder species, and the cancer species of Akt over-expressing cancer. Because applicant did not state that the election was with traverse and did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-75 are pending. Claims 43-75 are canceled. Claims 27-40 are withdrawn by Applicants. Claim 24 is withdrawn from consideration for being drawn to a non-elected species. Claims 12-23, 25, 26, 41, and 42 are currently under prosecution.

Specification

2. The disclosure is objected to because of the following informalities: There are blanks on pages 30 and 81-85 for Application numbers that are referenced to. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 12-23, 25, 26, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of laboratory designations only to identify a particular protein such as "Bik polypeptide" renders the claims indefinite because different laboratories may use the same laboratory designation to define completely distinct proteins or protein fragments. Amendment of the claims, for example, to include the **SEQ ID number** which unambiguously defines a given protein, would obviate the rejection.

4. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claimed method of comprising administering to a cell a Bik polypeptide having an amino acid substitution lacks steps and objectives.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-23, 25, 26, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are drawn to a method comprising administering to a cell a Bik polypeptide having an amino acid substitution (claims 12, 25, 26, 41), wherein the amino acid substitution is both Thr^{33} and Ser^{35} (claim 13, 17-23), wherein the substitution is a Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitution (claims 14 and 15), wherein the polypeptide further comprises a transduction domain (claims 16), and the method of claim 13 further defined as comprising modifying the Bik polypeptide at both amino acid position 33 and amino acid position 35 wherein the modification results in an ability of the amino acid to be phosphorylated (claim 42).

The specification discloses that a Bik polypeptide comprising anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity, wherein the Bik comprises at least one altered amino acid compared to native Bik is a "mutant Bik" and the alteration of Bik may comprise a modified amino acid or substituted amino acid (p. 7). The specification discloses that mutations, either to similar amino acids or not, may be made anywhere in the Bik polypeptide and that some of these mutants will have the same activity as the exemplary embodiments provided in the specification. For example, threonine, serine, or other appropriate amino acids anywhere within Bik can be substituted. The specification discloses that the mutant Bik polypeptide may further comprise a transduction domain and lists non-limiting examples of a transduction domain such as HIV Tat or penetratin (p. 10). The specification discloses exemplary Bik polypeptides SEQ ID NO:3 and SEQ ID NO:4 (p. 9) and mutant Bik SEQ ID NO:9,

which comprises the same sequence as SEQ ID NO:3 except it comprises the Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions (p. 9 and 16). The specification does not disclose **any other Bik polypeptides**, or **any Bik** having an amino acid substitution with **any amino acid at any position, any amino acids substituted** at position 33 and 35, **any Bik** having Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions, **any Bik** polypeptide comprising **any** transduction domain, or **any Bik** comprising **any modification** at position 33 and 35 that results in an inability of the amino acid to be phosphorylated, as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of **"a Bik polypeptide having an amino acid substitution", "wherein the amino acid substitution is both Thr^{33} and Ser^{35}", "wherein the substitution is a Thr^{33} to Asp^{33}", "wherein the substitution is a Ser^{35} to Asp^{35}", "comprises a transduction domain"**, or **"modifying the Bik polypeptide...wherein the modification results in the inability of the amino acid to be phosphorylated".** Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a

recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a Bik polypeptide having an amino acid substitution, a transduction domain or modification, per Lilly by structurally describing representative Bik polypeptides having an amino acid substitution, transduction domain, or modification or by describing "structural features common to the members of the genus, which features constitute a

substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe a Bik polypeptide having an amino acid substitution, a transduction domain or modification useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses exemplary Bik polypeptides SEQ ID NOs:3 and 4 and mutant Bik polypeptide SEQ ID NO:9, this does not provide a description of the broadly claimed Bik polypeptides having an amino acid substitution, a transduction domain or modification that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe a Bik polypeptide having an amino acid substitution, a transduction domain or modification by the test set out in Lilly because the specification describes only exemplary Bik polypeptides SEQ ID NOs:3 and 4 and mutant Bik polypeptide SEQ ID NO:9. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of a Bik polypeptide having an amino acid substitution, a transduction domain or modification that is required to practice the claimed invention. Since the specification fails to

adequately describe the product to which the claimed method of administering to a cell uses, it also fails to adequately describe the method.

6. Claims 12-23, 25, 26, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 12-23, 25, 26, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method of inducing apoptosis in a cultured cell comprising administering to a cultured cell a Bik polypeptide having the amino acid sequence SEQ ID NO:9 and comprising a transduction domain allowing the Bik polypeptide to internalize**, does not reasonably provide enablement for **a method comprising administering to a cell a Bik polypeptide having an amino acid substitution.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not

'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method comprising administering to a cell a Bik polypeptide having an amino acid substitution (claims 12), wherein the amino acid substitution is both Thr^{33} and Ser^{35} (claim 13), wherein the substitution is a Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitution (claims 14 and 15), wherein the polypeptide further comprises a transduction domain (claims 16), wherein the cell is comprised in an animal and the animal is a human (claims 17 and 18), wherein the human has a proliferative cell disorder and the disorder is cancer (claim 19-23), wherein the polypeptide is comprised in pharmacologically acceptable excipient (claim 25), wherein the polypeptide is complexed with a lipid (claim 26), the method of claim 12 further defined as a method of preventing growth of a cell in an individual (claim 41), and the method of claim 13 further defined as comprising modifying the Bik polypeptide at both amino acid position 33 and amino acid position 35 wherein the modification results in an ability of

the amino acid to be phosphorylated (claim 42). The claims are broadly drawn to administering a Bik polypeptide having an amino acid substitution to a cell **both *in vivo* and *in vitro***, wherein the polypeptide has **any** amino acid substitution, or **any** substitution at positions Thr^{33} and Ser^{35}, or **no means of internalizing**.

The specification discloses a novel therapeutic Bik mutant for cancer and that mutant forms of Bik exert strong antitumor activity both *in vivo* and *in vitro*. The specification contemplates methods for inhibiting proliferation in a cancer and/or tumor cell comprising contacting the cell with a mutant Bik polypeptide in an amount effective to inhibit cellular proliferation (p. 3, p. 10-11, and Example 12, p. 86). The specification discloses substituting Bik residues Thr^{33} and Ser^{35} with aspartate (Examples 1 to 3, and 6) to produce a mutated Bik nucleic acid for inoculation of the gene into mice with successful results *in vivo* to reduce tumor volume and *in vitro* to induce apoptosis.

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide guidance or working examples for administering a Bik **polypeptide** having an amino acid substitution to a cell *in vivo* or *in vitro* that successfully exerts antitumor activity, pro-apoptotic activity, and/or inhibits cell proliferation as contemplated by the specification. The specification provides only examples of administering a Bik **polynucleotide** through transfection of cells (p. 75) or lipid delivery to mice (p. 77). Therefore, one of skill in the art would not know how to predictably use a Bik polypeptide having an amino acid substitution for both *in vivo* and *in vitro* antitumor activity or inhibiting cellular proliferation by administering the polypeptide to a cell.

Mathai et al (J of Biological Chemistry, 2005, 280, 23829-23836) teach that Bik is located at the endoplasmic reticulum from where it elicits pro-apoptotic signals and, given sufficient time, these signals lead to cell death by pathway(s) (p. 23835). Clearly, Bik can only initiate apoptosis if it is inside the cell. Given that Bik requires intracellular initiation of apoptosis, one could not predictably induce apoptosis by administration of a mutant Bik polypeptide to a cell because the polypeptide would be external to the cell and unable to induce apoptosis. Claim 16 is the only claim drawn to administering to a cell a mutant Bik polypeptide comprising a transduction domain that would allow the Bik polypeptide to internalize.

More factors must be considered in addition to internalizing a protein when administering to a cell to induce apoptosis, inhibit cellular proliferation, or exert anti-tumor effects. One factor is targeting the protein to a specific tissue or cell type such as a tumor cell so that surrounding normal tissues are not damaged by the protein's effects. Another factor to consider is the development of an immune response against a mutant polypeptide that is not found naturally occurring in an animal. Administration of an unnaturally occurring protein may induce an immune response against the protein and prevent the protein from reaching its target. Azar et al teach (Apoptosis, 2000, 5:531-542), that the design of specific targeting reagents/drugs still remains the major goal in the treatment of neoplastic diseases and the main aim is to direct therapeutic agents into tumor cells, while avoiding damage to normal tissues and without evoking an immune response (p. 531, col. 1). Azar et al teach the successful targeting of a chimeric Bik protein joined to Gonadotropin releasing hormone (GnRH) that targets

adenocarcinomas. Targeting Bik to the cells induced apoptosis *in vitro* in adenocarcinoma cell lines (abstract, p. 533, col. 2; p. 541, col. 2).

Azar et al address the problems of administering their chimeric Bik protein *in vivo*. The reference teaches that the immunogenicity of targeting proteins constitutes a problem to which no practical solution has been found. Azar et al teach that human chimeric proteins that incorporate a human apoptosis-inducing agent, such as Bik, may decrease immunogenicity problems because the apoptosis-inducing agent is of human origin is expected to display reduced immunogenicity in recipients (p. 539, col. 1 and 2; p. 541, col. 2). However, the claims are drawn to a mutant Bik polypeptide that is not the wild-type form and the mutant form may elicit an immune response against the polypeptide, hence, clearing the polypeptide from the animal's body and preventing it from functioning. Given the teaching of Azar et al and Mathai et al, one of skill in the art could not administer a Bik polypeptide having an amino acid substitution to a cell and predictably induce apoptosis, inhibit cellular proliferation, or exert anti-tumor effects as contemplated by the specification.

Regarding any substitution at positions Thr^{33} and Ser^{35}, one could not predictably induce apoptosis, inhibit cellular proliferation or exert anti-tumor effects using a Bik polypeptide with any substitutions or any substitutions at positions Thr^{33} and Ser^{35}. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allows them to function. Bowie et al further teach that certain positions in the sequence are critical to the three

dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (p. 1306, cols 1 and 2). Clearly, the three dimensional structure of a protein is critical to its function, particularly relating to the induction of apoptosis, inhibition of cellular proliferation or anti-tumor effects. However, neither the specification nor the art of record provide teachings that provide information about the effects any amino acid substitution would have or any amino acid substitution at positions Thr^{33} and Ser^{35} would have on its activity. This information appears to be critical because the art recognizes (see Bowie et al above) that it is the protein sequence that determines the three dimensional shape of a protein and suggests that the three-dimensional structure of the protein molecule may be essential for the protein's function and ability to be modulated. Thus, in the absence of guidance in the specification, the effects of the undefined amino acid substitutions, it cannot be predicted and one could not determine how to practice the claimed invention or predict which of the whole universe of broadly claimed Bik polypeptides having an amino acid substitution anywhere or at positions Thr^{33} and Ser^{35} would function as claimed with a reasonable expectation of success.

Given the lack of guidance in the specification, no working examples which would provide guidance to one skilled in the art, the state of the art, the novel nature of the invention, and that no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as claimed and contemplated by the specification with a reasonable expectation of success, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Azar et al teach (Apoptosis, 2000, 5:531-542).

The claim is drawn to a method comprising administering to a cell a Bik polypeptide having an amino acid substitution.

Azar et al teach a Bik polypeptide joined to Gonadotropin releasing hormone (GnRH) to form a chimeric protein and the administration of the polypeptide to a cell (abstract; p. 532, col. 1 and 2; p. 541, col. 1 and 2). It would be expected that in the chimeric Bik polypeptide, an amino acid substitution exists in order to join the GnRH to the Bik polypeptide, hence all of the limitations of the claims are met.

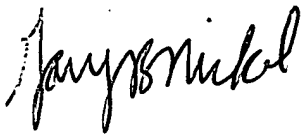
8. Conclusion: Claims 12-23, 25, 26, 41, and 42 are rejected.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642



GARY B. NICKOL, PH.D.
PRIMARY EXAMINER